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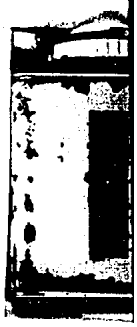

RECENT USSR WORK ON ETIOLOGY OF MALIGNANT TUMORS AND ANTITUMOR IMMUNITY

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Among the many theories pertaining to the etiology and pathogenesis of malignant tumors, the virus theory has been subjected to the most extensive study during recent years. The virus nature of some sarcomas of birds, of cancer of the lactic glands of mice, of cancer of the kidneys of leopard frogs, of rabbit papillomas, and of some human papillomas has been established. However, it has not been possible to isolate a filterable virus-like factor possessing cancerogenic activity from the majority of the tumors, including all malignant human tumors. At the same time, many facts speak in favor of the virus nature of nonfilterable tumors.

A. D. Timofeyevskiy, when investigating the explantates of some human tumors with the aid of an electron microscope, detected in the globular virus-like formations or bodies. Further investigation will answer the question as to the nature of these bodies. Such investigation is necessary because many extraeous viruses may effectively propagate in tumors.

L. A. Zil'ber and his collaborators showed with the aid of the anaphylaxis reaction that it is possible to detect in tumors an antigen which is distinct from the antigens of the normal organism. What is the nature of this antigen?

We still do not have convincing data which confirm the presence in the specific tumor antigen of a virus in addition to modified forms of proteins that are normally contained in the body.

Attempts to use known methods of culturing viruses succeeded only in the case of viruses of filterable tumors, i. e., in cases where the role of viruses in the development of the tumor had already been proven. On the other hand, experiments on the isolation and culturing of viruses from nonfilterable tumors proved to be unsuccessful or inconclusive as far as the results were concerned.

Obviously, a special method must be used for the isolation of viruses of nonfilterable tumors. In 1950-1951, together with T. Ya. Appazova, we attempted to develop such a method. The procedure we used consisted essentially in a special method of culturing combined with multiple passages through chick embryos. The possibility of the introduction of tumor cells into the chick embryos was rigidly excluded. A number of experiments was carried out in such a manner that after each passage, the material was filtered through Seitz filters and the filtrate used for the subsequent passage.

The experiments were carried out on Brown-Pierce rabbit cancer. This tumor is one of the most malignant and is of particular interest for experiments of this type. It is easily transferred by inoculation, metastasizes within a short period of time into all inner organs, and kills the animals within a short time. This tumor cannot be transmitted by using filtrates. Attempts to isolate from it a virus which has a cancerogenic effect proved unsuccessful.

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The material derived from different passages through chicken embryos of the cell-free factor of this tumor was introduced into rabbits to determine its cancerogenic activity. More than 350 rabbits were used in this work. The experiments demonstrated that the material derived from the early passages does not exhibit any cancerogenic activity. However, after five to seven blind passages had been carried out, cancerogenic activity appeared, in a number of experiments, in material derived from relatively late passages up to the 30's.

In view of the fact that the transmission of tumor cells was doubtless excluded in the passages and that tumor cells were found to be absent by carrying out a great number of microscopic observations for purposes of control (more than 5,000 smears were examined), only one conclusion can be made on the basis of these experiments: a filterable factor of the Brown-Pierce tumor was cultured, and this factor has the capacity to bring about the growth of a tumor when introduced into rabbits.

What is the nature of this factor?

With the aid of an electron microscope, an answer to thic question can be received by investigating the material derived from passages. In the material examined, globular bodies having dimensions of 50-150 millimicrons were found. These bodies were similar to those formed by known pathogenic viruses. They were not found in control material derived from uninfected embryos; only in individual cases, were single bodies observed in the control material which resembled those found in material that had cancerogenic activity.

Thus, there are sufficient reasons to assume that the factor which has been cultured is a tumor virus, without prejudicing the answer to the problem as to whether this factor is of an exogenic or endogenic nature.

In 1952, these data were checked and verified by a special commission appointed by the Ministry of Health USSR and by the Academy of Medical Sciences USSR. On the basis of a decision made by the Presidium of the Academy of Medical Sciences USSR, the Institute of Epidemiology and Microbiology imeni N. F. Gamaleya checked our experiments again in 1954.

At this institute several passages of the factor of Brown-Pierce tumors were carried out according to our method. Material derived from the 8th, 10th, 12th, and 18th passages, which definitely did not contain tumor cells and had been filtered 7 to 17 times through Seitz filters, proved to be capable of inducing Brown-Pierce tumors in rabbits. The question arises as to whether this method is applicable to other nonfilterable tumors, the virus nature of which has not been established.

Of special interest in this respect are tumors induced by cancerogenic substances. Hitherto, it has not been possible to prove the presence of specific viruses in neoplasms of this type. The problem acquires a special importance in view of the fact that a number of human tumors is unquestionably induced by cancerogenic substances and cancerogenic [physical] effect. The limited data at our disposal indicate that it is possible to use our method as far as some of these tumors are concerned.

We have carried out experiments with the spindle-shaped cell sarcoma of rats brought about by the introduction of methycholanthrene and with the osteosarcoma originating in rats as a result of the introduction of one of the radioactive elements.

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The material derived from different passages was investigated by means of an electron microscope. In these investigations, virus-like bodies were regularly detected. These bodies were similar to those found in material derived from Brown-Pierce tumors. By introducing the material investigated in this instance, which definitely did not contain any cells, it was possible to induce tumors in rats.

If these facts are confirmed by further investigation, the solution of the problem concerning the nature of tumors brought about by cancerogenic substances will be advanced considerably.

By the same method, experiments were carried out with human tumors. As initial material for culturing the virus, cancers of the stomach and of the lactic gland were used. Forty-seven gastric tumors of diverse histological structure and five tumors of the lactic gland were used. More than 500 passages were carried out with the use of 4,000 chick-embryos.

Material derived from different passages was again studied with the aid of an electron microscope. The results were similar to those obtained in the electronmicroscopic investigation of material from Brown-Pierce tumors and of induced sarcomas of rats: in the different passages up to the 60th, the same virus-like bodies were observed. These observations were made by using material derived from gastric cancers.

However, it is impossible to draw conclusions regarding the nature of a virus on the basis of morphological data alone. If the substance under investigation is actually a virus which participates in the development of the tumor process, antibodies active against this virus must be present in the organism of the patient, just as they are present in other virus diseases. To check this assumption, immunological reactions were carried out with material derived from different passages. These reactions were carried out on patients with and without tumors. It was established that in the group of patients with tumors antibodies active against the cultured virus of gastric cancer were always present. In other diseases (tuberculosis, chronic inflammatory and supporative conditons, and various infections) as well as in pregnancy, such antibodies were detected only in an insignificant number of cases.

This regularity with respect to the occurrence of antibodies, which has been established on a great number of patients, enables us to draw two important conclusions:

The first conclusion is that a virus can be isolated from human tumors (cancer of the stomach) can be cultured by our method on chick embryos, and antibodies with reference to it can be detected in the organism of patients. The detection of the antibodies is an indirect proof of the participation of the virus in the development of the tumor process, a proof which makes it possible to assert that the virus of human cancer has been cultured. The importance of these data is obvious, provided that further investigation will confirm their validity.

The second conclusion, which is no less important from the practical standpoint, is that specific antibodies are present in the organism of patients who have tumors. This finding makes it possible to raise the question in regard to diagnosing immunologically the presence of malignant tumors. If the virus is actually effective in inducing the tumor, then the exclusion of this virus from the chain of the processes of cancerogenesis by creating an antivirus immunity will prevent the development of the tumor.

However, this hypothesis cannot be checked with nonfilterable tumors, because in order to create anti-virus immunity, a virus is needed. Thus, the

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prophylaxis of tumors is closely connected with the development of a satisfactory method for the isolation of tumor viruses. Actually, it has been shown that inoculation of rabbits with vaccine derived from the material of the first passage induces on the average in 50 percent of the animals a pronounced immunity to a cellular inoculation with the tumor. This immunity was induced notwithstanding the fact that the material used for immunization did not contain any tumor cells.

Quite unexpected was another result. The vaccination of rabbits with the vaccine derived from late passages, i.e., with virus vaccine, proved to be much more effective. While the vaccine of the first passage produced immunity only in 50 percent of the animals, the virus vaccine derived from late passages produced a very strong immunity in practically all the animals vaccinated. What is the mechanism of the immunization? It is difficult to decide at present whether our vaccine acts like all live vaccines, i.e., induces a vaccine process which results in immunity, or produces immunity by a different mechanism. Even though the immunity may be of the type induced by a vaccine process, the value of the vaccine is no less for that reason, because all live vaccines act in this manner and are nevertheless very effective.

Furthermore, a formalinized vaccine also proved to be effective in a number of experiements. This vaccine did not bring about a tumor process which was morphologically detectable, a fact that could be confirmed in a control experiment.

Our meager data on the subject indicate that the virus vaccine is also effective whith reference to rat tumors. For instance, experiments established that inoculation with a sarcoma brought about the growth of a tumor in only four of 25 vaccinated rats. Other experiments furthermore showed that out of 25 rats vaccinated with material from normal chick embryos, the inoculation of sarcoma proved to be successful in 17 cases. Thus, our method made it possible to isolate the virus from rabbit cancer and from sarcoma of rats induced by cancerogenic substances, i.e., tumors the virus nature of which has not been regarded as established heretofore.

Numerous data indicate that it is possible to use our method for the isolation of a virus-like agent from human gastric cancer, an agent with reference to which antibodies can be detected in patients who have malignant tumors. This result makes feasible the development of a method for the immunological diagnosis of cancer. Continuation of the clinical tests started in 1952 will enable us to form a definite opinion in regard to the possibility of exerting action on the process of the development of tumors in human beings. It is obvious that many problems which have not yet been completely solved remain in this field. The united efforts of specialists in various branches of science are needed for the solution of these problems.

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